Chapter 21
Lipid Metabolism

SUMMARY

Section 21.2

- Fatty acids are activated and transported to the mitochondrial matrix for further catabolism.
- The breakdown of fatty acids takes place in the mitochondrial matrix and proceeds by successive removal of two-carbon units as acetyl-CoA. Each cleavage of a two-carbon moiety requires a four-step reaction sequence called β-oxidation.

Section 21.3

- The complete oxidation of fatty acids by the citric acid cycle and the electron-transport chain releases large amounts of energy.
- When we include the reoxidation of NADH and $FADH_2$ from β-oxidation and the citric acid cycle, we obtain a net yield of 120 ATP for a single molecule of stearic acid.

Section 21.4

- Fatty acids with uneven numbers of carbon atoms produce propionyl-CoA in the last round of β-oxidation. Propionyl-CoA can be converted to succinyl-CoA, which plays a role in the citric acid cycle.
- The oxidation of unsaturated fatty acids requires enzymes that catalyze isomerization around the double bonds so that oxidation can proceed.

Section 21.5

- If an organism has an excess of acetyl-CoA, it produces substances related to acetone, thus the name “ketone bodies.”
- This situation can arise from an excessive intake of fats compared to carbohydrates, or from diabetes.

Section 21.6

- Acetyl-CoA is transported to the cytosol and converted to malonyl-CoA. Chain lengthening takes place in the cytosol as well.
- The biosynthesis of fatty acids proceeds by the addition of two-carbon units to the hydrocarbon chain. The process is catalyzed in many organisms by a large multienzyme complex called fatty acid synthase.

Section 21.7

- Most compound lipids such as triacylglycerols, phosphoacylglycerols, and sphingolipids, have fatty acids as precursors.
- Fatty acids are linked to a backbone molecule, such as glycerol for triacylglycerols or phosphoacylglycerols, or sphingosine for sphingolipids. Other moieties are added to give rise to specific compounds.

Section 21.8

- The biosynthesis of cholesterol proceeds by the condensation of five-carbon isoprenoid units.
- Isoprenoid units in turn are derived from the reaction of three acetyl-CoA units.
- Once cholesterol is formed, it serves as the precursor for other steroids.
- Cholesterol must be packaged for transport in the bloodstream. Some of these forms of cholesterol play a role in heart disease.

Section 21.9

- Accumulation of fats in tissues, especially as fat cells (adipocytes) gives rise to overweight and obesity, which, in turn, lead to drastic health problems such as diabetes, heart attacks, and strokes. In addition obesity can predispose to some kinds of cancer
- Hormones from the brain, stomach, intestines, pancreas, and adipose tissue all play a role in stimulating and in repressing appetite.
- Two sets of neurons play a role. One set of neurons produces a protein that leads to increased eating, and the other set gives rise to products that depress eating
- The neurons that stimulate eating are called the NPY/AgRP-producing neurons.
- The neurons that tend to inhibit eating produce melanocortins, another class of peptide hormones. The neurons that suppress appetite have receptors for melanocortin and one of several kinds of receptors for NPY, as well as for other hormones such as insulin or leptin. The neurons that stimulate appetite have various kinds of NPY receptors, as well as receptors for insulin and other hormones
- The peptide hormones ghrelin and cholecystokinin are the main regulators of short-term effects. Ghrelin is produced in the stomach, primarily when the stomach is empty. Production of ghrelin is a hunger signal and falls off as food is eaten.
- Cholecystokinin is the signal for satiety, and so its effect is the opposite of that produced by ghrelin. Cholecystokinin and ghrelin together modulate behavior over the short term, but they do not act alone. Their activity is also modulated by the long-term control system.
- Insulin and leptin are the hormones most deeply involved in long-term control of eating behavior

LECTURE NOTES

This chapter deals with both lipid catabolism and anabolism, allowing for direct comparison of the two processes. The information will likely be new to students; however, they are apt to find it interesting as it expands their knowledge of metabolism in a way that they will easily see as practical. This chapter will probably require two lectures, one for catabolism, and the second for anabolism.

LECTURE OUTLINE

I. Catabolism of lipids
    A. Lipases and phospholipases
    B. Role of coenzyme A
    C. Role of carnitine
    D. β-oxidation
        1. Oxidation yielding $FADH_2$
        2. Hydration
        3. Oxidation yielding NADH
        4. Thiolytic cleavage
II. Energy yield from the oxidation of fatty acids
III. Catabolism of unsaturated fatty acids and odd-carbon fatty acids
    A. Odd-numbered fatty acids yield priopionyl-CoA
        1. Path leads to succinyl-CoA
        2. Use of vitamin B12
    B. Monounsaturated fatty acids – cis/trans isomerization
    C. Polyunsaturated fatty acids
        1. 2,4-dienoyl-CoA reductase, use of NADPH
        2. cis/trans isomerization
IV. Ketone bodies
V. Fatty acid biosynthesis
    A. Sources of acetyl-CoA
    B. Use of NADPH vs. NADH
    C. Production of malonyl-CoA
    D. Fatty acid synthase
        1. Production of palmitate
        2. Use of acyl carrier protein
        3. Condensation
        4. Reduction
        5. Dehydration
        6. Reduction
        7. Repetition of cycle
    E. Essential fatty acids
    F. Comparison of catabolism with anabolism
VI. Synthesis of acylglycerols and compound lipids
    A. Triacylglycerols
    B. Phosphoacylglycerols
    C. Sphingolipids
VII. Cholesterol biosynthesis
    A. Role of HMG-CoA
    B. Other steroids
    C. Cholesterol and heart disease
VIII. Hormonal Control of Appetite
    A. Hormones that play a role

B. Long-term effects
C. Short-term effects

ANSWERS TO PROBLEMS

21.1 Lipids Are Involved in the Generation and Storage of Energy

1.

(a) For mobile organisms—such as a migrating hummingbird—weight can be a critical factor, and packing the most energy into the least weight is decidedly advantageous. A 2.5-g hummingbird needs to add about 2 g of fat for migration energy, which would increase body weight by 80%. The equivalent amount of energy stored as glycogen would be about 5 g, which would increase its body weight by 200%; the bird would never get off the ground!

(b) For immobile plants, weight is not a critical factor, and it takes more energy to make fat or oil than it does to make starch. (The second law of thermodynamics would dictate that the energy obtained from oil would be less than that expended making oil. You can verify this numerically if you wish.) In the case of plant *seeds,* "compact" energy is beneficial, because the seed must be self-sufficient until enough growth has occurred to permit photosynthesis.

21.2 Catabolism of Lipids

2. Phospholipase A_1 hydrolyzes the ester bond to carbon-1 of the glycerol backbone; phospholipase A_2 hydrolyzes the ester bond to carbon-2 of the backbone.

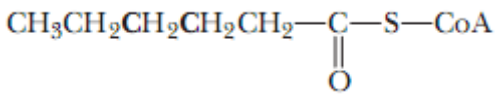
3. A hormone signal activates adenylate cyclase, which makes cAMP. This activates protein kinases, which phosphorylate the lipases, thereby activating them.

4. Acyl-CoAs are high-energy compounds. An acyl-CoA has sufficient energy to initiate the β-oxidation process. The CoA is also a tag indicating that the molecule is destined for oxidation.

5. Acyl groups are esterified to carnitine to cross the inner mitochondrial membrane. There are transesterification reactions from the acyl-CoA to carnitine and from acylcarnitine to CoA (see Figure 21.5).

6. Acyl-CoA dehydrogenase removes hydrogens from adjacent carbons, creating a double bond and using FAD as coenzyme. β-Hydroxy-CoA dehydrogenase oxidizes an alcohol group to a ketone group and uses NAD^+ as a coenzyme.

7.



The two carbons shown in boldface type are the ones that will have the double bond between them. The orientation will be *trans.*

8. Seven carbon–carbon bonds are broken in the course of β-oxidation (see Figure 21.6).

9. In the liver, glycogen breakdown and gluconeogenesis would occur. In the muscle, glycogen breakdown and glycolysis would occur.

21.3 The Energy Yield from the Oxidation of Fatty Acids

10. One obtains 6.7 ATP per carbon and 0.42 ATP per gram for stearic acid versus 5 ATP per carbon and 0.17 ATP per gram for glucose. More energy is available from stearic acid than from glucose.
11. The processing of the acetyl-CoA through the citric acid cycle and the electron transport chain produces more energy than the processing of the NADH and $FADH_2$ produced during β-oxidation.
12. From seven cycles of β-oxidation: 8 acetyl-CoA, 7 $FADH_2$, and 7 NADH. From the processing of 8 acetyl-CoA in the citric acid cycle: 8 $FADH_2$, 24 NADH, and 8 GTP. From reoxidation of all $FADH_2$ and NADH: 22.5 ATP from 15 $FADH_2$, 77.5 ATP from 31 NADH. From 8 GTP: 8 ATP. Subtotal: 108 ATP. A 2-ATP equivalent was used in the activation step. Grand total: 106 ATP. The grand total for stearic acid was 120 ATP.
13. The humps of camels contain lipids that can be degraded as a source of metabolic water, rather than water as such.

21.4 Catabolism of Unsaturated Fatty Acids and Odd-Carbon Fatty Acids

14. For an odd-chain fatty acid, β-oxidation proceeds normally until the last round. When five carbons are left, that round of β-oxidation releases one acetyl-CoA and one propionyl-CoA. Propionyl-CoA cannot be further metabolized by β-oxidation; however, a separate set of enzymes converts propionyl-CoA into succinyl-CoA, which can then enter the citric acid cycle.
15. False. The oxidation of unsaturated fatty acids to acetyl-CoA requires a *cis–trans* isomerization and an epimerization, reactions that are not found in the oxidation of saturated fatty acids.
16. For a monounsaturated fatty acid, an additional enzyme is needed, the enoyl-CoA isomerase.
17. For a polyunsaturated fatty acid, two additional enzymes are needed, the enoyl-CoA isomerase and 2,4-dienoyl-CoA reductase.
18. From seven cycles of β-oxidation: 7 acetyl-CoA, 1 propionyl-CoA, 7 $FADH_2$, 7 NADH. From the processing of 7 acetyl-CoA in the citric acid cycle: 7 $FADH_2$, 21 NADH, and 7 GTP. From the processing of the propionyl-CoA: –1 ATP for conversion to succinyl-CoA, –1 GTP from the citric acid cycle, and 1 NADH and 1 $FADH_2$ from the citric acid cycle. From reoxidation of all $FADH_2$ and NADH: 22.5 ATP from 15 $FADH_2$, and 72.5 ATP from 29 NADH. From 8 GTP: 8 ATP. Subtotal: 103 ATP. Subtract a 2-ATP equivalent used in activation step and a 1-ATP equivalent used in the conversion to succinyl-CoA for a grand total of 100 ATP.
19. An 18-carbon saturated fatty acid yields 120 ATP. For a monounsaturated fatty acid, the double bond eliminates the step that produces $FADH_2$, so there would be 1.5 ATP less for oleic acid, or 118.5 ATP total.
20. An 18-carbon saturated fatty acid yields 120 ATP. For a diunsaturated fatty acid with the bonds in the Δ^9 and Δ^{12} positions, the first double bond eliminates an $FADH_2$. The second double bond uses an NADPH, which we are guessing is the same cost as using an NADH. Thus a total of 4 ATP are lost, compared with a saturated fatty acid, so the total is 116 ATP.

21. It would take seven cycles of β-oxidation to release 14 carbons as acetyl-CoA, with the last three being released as propionyl-CoA.
22. Fats cannot produce a net yield of glucose because they must enter the citric acid cycle as the two-carbon unit acetyl-CoA. In the first few steps, two carbons are released as CO_2. However, an odd-chain fatty acid can be considered partially glucogenic because the final three carbons become succinyl-CoA and enter the citric acid cycle after the decarboxylation steps. Thus, if an extra succinyl-CoA is added, it can then be drawn off later as malate and used for gluconeogenesis without removing the steady-state level of citric acid cycle intermediates.

21.5 Ketone Bodies

23. Ketones are produced when there is an imbalance in lipid catabolism, compared with carbohydrate catabolism. If fatty acids are being β-oxidized to produce acetyl-CoA, but there is insufficient oxaloacetate because it is being drawn off for gluconeogenesis, the acetyl-CoA molecules combine to form ketone bodies.
24. Two acetyl-CoA molecules combine to form acetoacetyl-CoA. This can then release coenzyme A to yield acetoacetate, which can be converted either to β-hydroxybutyrate or to acetone.
25. If the reason for passing out is uncontrolled diabetes, the doctor expects to smell acetone on the breath, since the otherwise unused sugars are being converted to fats and ketone bodies.
26. Ethanol is converted to acetaldehyde and then to acetic acid. Humans can use that acetic acid only for energy, or they can convert it to fatty acids and other lipids.
27. The metallic taste may be due to acetone, which means that your friend may have a mild state of ketosis. Ask if your friend has consulted a doctor about the diet regimen, and perhaps recommend either backing off from such a low-calorie diet or drinking more water to flush the system more thoroughly.

21.6 Fatty-Acid Biosynthesis

28. The two pathways have in common the involvement of acetyl-CoA and thioesters, and each round of breakdown or synthesis involves two-carbon units. The differences are many: malonyl-CoA is involved in biosynthesis, not in breakdown; thioesters involve CoA in breakdown and involve acyl carrier proteins in biosynthesis; biosynthesis occurs in the cytosol, but breakdown occurs in the mitochondrial matrix; breakdown is an oxidative process that requires NAD^+ and FAD and produces ATP by electron transport and oxidative phosphorylation, whereas biosynthesis is a reductive process that requires NADPH and ATP.
29. Step 1: biotin is carboxylated using bicarbonate ion (HCO_3^-) as the source of the carboxyl group. Step 2: the carboxylated biotin is brought into proximity with enzyme-bound acetyl-CoA by a biotin carrier protein. Step 3: the carboxyl group is transferred to acetyl-CoA, forming malonyl-CoA.
30. It is a molecule that commits itself to fatty-acid synthesis. It is also a potent inhibitor of carnitine acyltransferase I, thereby shutting down β-oxidation.
31. ACP, citrate, cytosol, *trans* double bonds, D-alcohols, β-reduction, NADPH, malonyl-CoA (except for one acetyl-CoA), and a multifunctional enzyme complex.

32. In β-oxidation, FAD is the coenzyme for the first oxidation reaction, while NAD^+ is the coenzyme for the second. In fatty-acid synthesis, NADPH is the coenzyme for both. The β-hydroxy-acyl group in β-oxidation has the L-configuration, while it has the D-configuration in fatty acid synthesis.
33. Both have a phosphopantetheine group at the active end. In coenzyme A, this group is attached to 2′-phospho-AMP; in ACP, it is attached to a serine residue of a protein.
34. ACP is a molecule that earmarks acyl groups for fatty-acid synthesis. It can be managed separately from acyl-CoA groups. Also, the ACP attaches to the acyl groups like a “swinging arm” that tethers it to the fatty-acid synthase complex.
35. Linoleate and linolenate cannot be synthesized by the body and must therefore be obtained from dietary sources. Mammals cannot produce a double bond beyond carbon atom 9 of fatty acids.
36. Acyl-CoA intermediates are essential in the conversion of fatty acids to other lipids.
37. Acetyl groups condense with oxaloacetate to form citrate, which can cross the mitochondrial membrane. Acetyl groups are regenerated in the cytosol by the reverse reaction.
38. If acetyl-carnitine forms in the matrix of the mitochondrion, it can be translocated to the cytosol via the carnitine translocase. Thus, this could represent another way of shuttling acetyl units out of the mitochondria for synthesis.

39. Energy is needed to condense an acetyl group to the growing fatty acid. In theory, such could be done with acetyl-CoA, using ATP. In practice, the ATP is used to convert acetyl-CoA to malonyl-CoA; the condensation of the acetyl moiety of malonyl-CoA is driven in part by the accompanying decarboxylation and requires no additional energy. A possible reason for this is to avoid a metabolic confusion of pathways, perhaps particularly important in (uncompartmented) prokaryotes; one could envision an acetyl-CoA from degradation being used immediately for synthesis. Malonyl-CoA says "synthesis"; acetyl-CoA says "degradation."

40.

(a) The lipoate "swinging arm" of the pyruvate dehydrogenase complex.

(b) The "arm" or ACP carries the group to be acted on from one enzyme to another (avoiding a diffusion-limited process and also positioning key groups correctly). In the case of the ACP, the group to be acted on (β-carbon) is always the same distance from the ACP, regardless of the length of the growing fatty acid, and thus the critical group is always in proximity to the active sites of the several pertinent enzymes.

21.7 Synthesis of Acylglycerols and Compound Lipids

41. The glycerol comes from degradation of other acylglycerols or from glycerol-3-phosphate derived from glycolysis.
42. The activating group found on the acylglycerol is cytidine diphosphate.
43. In prokaryotes, CTP reacts with phosphatidic acid to give a CDP-diacylglycerol. This reacts with serine to give phosphatidylserine, which decarboxylates to phosphatidylethanolamine. In eukaryotes, CDP-ethanolamine reacts with a diacylglycerol to give phosphatidylethanolamine.

21.8 Cholesterol Biosynthesis

44. In steroid biosynthesis, three acetyl-CoA molecules condense to form the six-carbon mevalonate, which then gives rise to a five-carbon isoprenoid unit. A second and then a third isoprenoid unit condense, giving rise to a 10-carbon and then a 15-carbon unit. Two of the 15-carbon units condense, forming a 30-carbon precursor of cholesterol.
45. See Figure 21.24.
46. Bile acids and steroid hormones.
47. All steroids have a characteristic fused-ring structure, implying a common biosynthetic origin.
48. One oxygen atom from O_2 is needed to form the epoxide. The NADPH is needed to reduce the other oxygen atom to water.
49. Cholesterol is nonpolar and cannot dissolve in blood, which is an aqueous medium.
50. Bile salts are made from cholesterol, and cholesterol is taken from the body into the intestine in the bile fluid.

21.9 Hormonal Control of Appetite

51. Neuropeptide Y operates in the central nervous system. Its function is to start a chain of events that stimulates appetite.
52. Melanocortins stimulate a chain of events that suppress appetite.
53. Ghrelin is a peptide hormone that serves as a hunger signal. Cholecystokinin has the opposite effect.
54. Leptin stimulates breakdown of lipids and inhibits fatty acid production.
55. Insulin stimulates production of leptin in adipocytes. In addition, f body fat decreases as a result of decreased appetite, the levels of insulin and leptin in the blood also decrease.